



1c678 U.S. PRO  
09/450609  
11/30/99

# Kongeriget Danmark

Patent application No.: PA 1998 01580

Date of filing: 01 Dec 1998

Applicant: Novo Nordisk A/S,  
Novo Allé  
DK-2880 Bagsværd

This is to certify the correctness of the following information:

The attached photocopy is a true copy of the following document:

- The specification, claims and abstract as filed with the application on the filing date indicated above.



**Patent- og  
Varemærkestyrelsen**  
Erhvervsministeriet

TAASTRUP 10 Nov 1999

*Lizzi Vester*

Lizzi Vester  
Head of Section

**New pharmaceutical composition and the process for its preparation**

5 The subject-matter of the present invention is a new pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione as active ingredient and the process for its preparation.

10 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione and pharmaceutically acceptable salts thereof has been found useful in the treatment of type 2 diabetes acting as a insulin sensitizer as disclosed in PCT Publication WO 97/41097.

The active ingredient is present as the base or as a pharmaceutically acceptable salt, preferably as the potassium salt.

15 Various solutions have been proposed for the preparation of medications based on 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione.

20 The aim of the present invention is to provide a new composition intended for the preparation of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione with improved stability, in particular solid dosage forms thereof.

25 It has been found in fact that 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione and its pharmaceutically acceptable salts may decompose in the presence of and in contact with water. Further it has been observed that decomposing may occur in the presence of oxygen.

30 Thus, from a first aspect, the subject-matter of the present invention is a pharmaceutical composition intended for the preparation of dosage forms and in particular solid dosage forms containing an efficacious quantity of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione or of one of its pharmaceutically acceptable salts as active ingredient.

The present invention is based on the surprising discovery of the fact that the stability of 5-  
[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-  
dione, or of one of its pharmaceutically acceptable salts, can be considerably improved in  
preparations containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-  
methyl]thiadiazolidine-2,4-dione or of its pharmaceutically acceptable salts and antioxidant  
agent if the product is composed of excipients which do not contain water.

Pharmaceutically acceptable salts forming part of this invention include salts such as alkali  
metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of  
organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, am-  
monium or substituted ammonium salts, aluminium salts. Salts may include acid addition  
salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates,  
hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methane-  
sulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates,  
glycerophosphates, ketoglutarates and the like.

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-  
dione, together with a conventional adjuvant, antioxidant carrier, or diluent, and if desired a  
pharmaceutically acceptable acid addition salt thereof, may be placed into the form of phar-  
maceutical compositions and unit dosages thereof, and in such form may be employed as  
solids, such as tablets or filled capsules, or oral powders to be diluted immediately before  
use filled with the same, all for oral use, in the form of suppositories for rectal administration;  
or as pessaries for vaginal use; or in the form of sterile injectable powders for parenteral,  
transdermal, nasal, pulmonary and ocular use.

Within the framework of the present description and of the claims, by powders is meant any  
mixture of components, granulated or not, intended to be placed in solution and/or in sus-  
pension in water, or again to be ingested directly or by any other appropriate means as for  
example in a mixture with a food product.

In accordance with a particular characteristic of the invention, the manufacture of tablets are  
carried out as a direct compression.

In accordance with another particular characteristic, this composition also contains pharmaceutically acceptable excipients.

5 In accordance with a particular characteristic of the invention, the antioxidant agent cited above is selected from among  $\alpha$ -tocopherol,  $\gamma$ -tocopherol,  $\delta$ -tocopherol, extracts of natural origin rich in tocopherol, L-ascorbic acid and its sodium or calcium salts, ascorbyl palmitate, propyl gallate (PG), octyl gallate, dodecyl gallate, butylated hydroxy anisole (BHA) and butylated hydroxy toluene (BHT).

10 In accordance with a currently preferred embodiment, the antioxidant agent will be  $\alpha$ -tocopherol.

In accordance with another particular characteristic of the invention, the diluent is lactose and/or cellulose microcrystalline, magnesium stearate, talc.

15 However, any other pharmaceutically acceptable diluents could be used if the diluents has a low water content.

20 The quantities of diluents can be easily determined by a person skilled in the art and depend of course on the final pharmaceutical form required.

Generally speaking, a composition which complies with the present invention and which are intended for the preparation of tablets, may contain, expressed in parts by weight per 100 parts of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-  
25 methyl]thiadiazolidine-2,4-dione, or of one of its pharmaceutically acceptable salts:

between 100 and 400,000 parts by weight of anhydrous lactose;  
between 1 and 100 parts by weight of an antioxidant;  
between 50 and 500 parts by weight of pregelatinized starch;  
30 between 1000 and 10,000 parts by weight of microcrystalline cellulose;  
between 10 and 500 parts by weight of crospovidone;  
between 10 and 500 parts by weight of silicon dioxide;  
between 10 and 500 parts by weight of hydrogenated vegetable oil;  
between 10 and 500 parts by weight of magnesium stearate;

between 10 and 500 parts by weight of hydroxypropyl methylcellulose;

between 10 and 500 parts by weight of hydroxypropyl cellulose;

between 1000 and 10,000 parts by weight of Mannitol;

between 10 and 500 parts by weight of stearic acid;

5 between 10 and 500 parts by weight of Titanium Dioxide;

According to a preferred embodiment of the invention the water content of the excipients is very low. More specifically the water content in the diluents is very low in order to minimize the water content of the pharmaceutical composition. Lactose is used in its anhydrous form.

10

Furthermore, all excipients may be applied in a dry form.

In accordance with a second aspect, the subject-matter of the present invention is a pharmaceutical preparation, in the form of tablet or powder, characterised in that it contains a

15 composition as defined previously associated if required with at least one customary additive selected from among the sweeteners, flavouring agents, colours and lubricants.

The choice of these additives and their quantity can easily be determined by a person skilled in the art.

20

Another manufacturing process for pharmaceutical compositions according to the invention is mixing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, one or more antioxidants and other pharmaceutical excipients followed by melt granulation in a high shear mixer. Hydrogenated, vegetable oil, waxes or other low temperature melting binders can be used. The granules can be filled into capsules, compressed into tablets or used in other pharmaceutical dosage forms.

25

More preferably the manufacturing process applied is direct compression of tablets, wherein 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, one or more antioxidants and other excipients suitable for direct compression are mixed followed by tableting.

30

Yet, another preferred embodiment of the manufacturing process is wet granulation, where granules are obtained by wet massing of 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-

quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, together with one or more anti-oxidants and other excipients.

It is assumed that the contact time with water have to be very short.

- 5 The most preferred process comprises the direct compression whereby 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione is kept at conditions of low water vapour pressure.

10 A sweetener may be a natural sugar such as sorbitol or a synthetic product such as saccharine or aspartame.

When the antioxidant selected is ascorbylpalmitat, propylgallat, which is a powder, it can be advantageous to mix it in an appropriate excipient such as  $\alpha$ -tocopherol succinat, lactose or cellulose micrycrystalline.

15

The present invention will further be illustrated with the following non-exhaustive examples.

In Example 1 through 4 the tablets were prepared according to the following procedure:

- 20 The active ingredient is mixed with cellulose microcrystalline in a drum mixer for 10 minutes. Lactose is added and the mixing continued for further two minutes. The lubricants are added and the mixing continued for further two minutes.

### EXAMPLE 1

25

25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 807227

- 30 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazoliny]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt, 003/97 9%  
Cellulose Microcrystalline 20%  
Lactose 66%  
Magnesium Stearate 0.5%  
Talc 4.5%

**EXAMPLE 2**

50 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt tablets 807237

5

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt, 003/97 18%

Cellulose Microcrystalline 20%

Mannitol 57%

10 Magnesium Stearate 0.5%

Talc 4.5%

**EXAMPLE 3**

15 50 mg 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 731725

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt 18%

20 Lactose 81.5%

Magnesium stearate 0.5%

**EXAMPLE 4**

25 0.25 mg 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt Tablets 728625

5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt 0.09%

30 Mannitol 98%

Magnesium stearate 2%

**EXAMPLE 5**

|   |                                                                                                                  |                                                                                                                         |
|---|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
|   | 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09%                                                                                                                   |
| 5 | Hydrogenated vegetable oil                                                                                       | 6.25%                                                                                                                   |
|   | Talc                                                                                                             | 5%                                                                                                                      |
|   | $\alpha$ -tocopherol                                                                                             | 50% of 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt |
|   | Lactose DCL21/Mannitol                                                                                           | Up to 200 g                                                                                                             |

10

The granulate is manufactured in a Baker Perkins 1 L high-shear mixer - using a water bath of 70°C. The mixing is carried out at 3000 RPM, chopper 6000 RPM and the granulation is performed at approx. 70°C. The hot granulate is sieved through sieve 1.25  $\mu$ m, and the cold granulate through sieve 1000  $\mu$ m. The glidant is added with a card for 2 min. The tablets are

15

In order to protect against light and improve the appearance of the tablets, the tablets are film-coated.

20 The tablets were coated with the following film-coating composition where an amount of coating material of 5 mg/cm<sup>2</sup> were chosen as being satisfactory with respect to stability of the tablets:

|    |                                                                                                                                                |                  |
|----|------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
|    | Methylhydroxypropylcellulose, Ph. Eur.....                                                                                                     | ~ 4.34 mg/tablet |
|    | Titanium Dioxide, Ph. Eur.....                                                                                                                 | ~ 1.73 -         |
| 25 | Purified Water, Ph. Eur.....                                                                                                                   | q.s. -           |
|    | Talc, Ph. Eur. (Added as polishing agent at the end of the film-coating process (0.5 % w/w of tablet core). Absorbed amount is not quantified. |                  |

**EXAMPLE 6**

30

|  |                                                                                                                  |       |
|--|------------------------------------------------------------------------------------------------------------------|-------|
|  | 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione, potassium salt | 0.09% |
|  | Povidone                                                                                                         | 7.5%  |
|  | Hydroxypropylmethyl cellulose                                                                                    | 1.5%  |



|                       |             |
|-----------------------|-------------|
| Croscarmellose sodium | 1.56%       |
| Talc                  | 1.1%        |
| Magnesium stearate    | 0.5%        |
| Lactose 300 mesh      | up to 200 g |

5

The granulate is manufactured by Baker Perkins 1 L intensive mixer. Dry mixing were carried out at 500 RPM, chopper 1500 RPM and granulation 1000 RPM and 2000 RPM. The wet granulate is sieved through sieve 1.25  $\mu\text{m}$  and the dry granulate through sieve 1000  $\mu\text{m}$ . The glidant is admixed with a card for 2 min. The tablets are manufactured by Diaf tablet machine with 9 mm punch.

10

#### EXAMPLE 7

15

Composition: Oral Powder, 1 mg/ml, 100 ml

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione potassium salt 0.1096 g  
 Mannitol 2.5 g  
 Hydroxypropyl- $\beta$ -cyclodextrin 10 g

20

To be diluted with 92 mL water before use.

#### EXAMPLE 8

25

Composition: Oral Powder, 10 mg/ml, 100 ml

30

5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione potassium salt 1.096 g  
 Mannitol 2.5 g  
 Hydroxypropyl- $\beta$ -cyclodextrin 10 g  
 Sodium Carbonate, anhydrous,  
 $\text{Na}_2\text{CO}_3$  15 mg

To be diluted with 92 mL water before use.



**CLAIMS**

1.      Pharmaceutical composition comprising
  - (a) 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-  
5   2,4-dione or a pharmaceutically acceptable salt thereof,  
and  
(b) optionally a pharmaceutically acceptable carrier.
2.      A composition according to claim 1 in the form of a tablet, a powder or a capsule.  
10
3.      A process for the preparation of a composition according to claim 1 or 2 which comprises the step of forming a mixture of:
  - (a) 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-  
2,4-dione or a pharmaceutically acceptable salt thereof,  
15 and  
(b) one or more pharmaceutically acceptable carriers.
4.      A process for the preparation of a composition according to claim 1 or 2 which comprises the following steps:
  - 20 (a) forming a mixture according to claim 3,  
and  
(b) direct compression of the mixture with excipients of a low water content .
5.      A process according to claim 3 or 4 characterized in that the steps are carried out at  
25 low water vapour pressure and low oxygen pressure.

**ABSTRACT**

The present invention provides a new stable pharmaceutical composition containing 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiadiazolidine-2,4-dione as  
5 active ingredient.

10

15